PCT/IB03/03113

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***814/Del/02*** *dated* ***2nd August 2002.***

Witness my hand this 3rd day of February 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

0814-2

02 AUG 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF ~~SHELF~~ STABLE TABLETS OF FOSINOPRIL SODIUM"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. PANANCHUKUNNATH MANOJ KUMAR

b. RAJEEV SHANKAR MATHUR

c. SANJEEV SETHI

d. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon - 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, PANANCHUKUNNATH MANOJ KUMAR, RAJEEV SHANKAR MATHUR, SANJEEV SETHI, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector 18, Udyog Vihar Industrial Area, Gurgaon-122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (PANANCHUKUNNATH MANOJ KUMAR)

b. (RAJEEV SHANKAR MATHUR)

c. (SANJEEV SETHI)

d. (RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. 683405 dated **20.07.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this 2ND day of **AUGUST, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM .2

0814-2

02 AUG 2002

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A PROCESS FOR THE PREPARATION OF SHELF STABLE TABLETS OF FOSINOPRIL SODIUM

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of shelf stable tablets of fosinopril sodium with or without diuretic(s).

Fosinopril sodium is an angiotensin converting enzyme inhibitor. Fosinopril sodium alone or in combination with thiazide diuretics is indicated for the treatment of hypertension. Fosinopril sodium is also used as an adjunctive therapy when added to conventional therapy including diuretics with or without digitalis for the management of heart failure.

Fosinopril sodium has low bulk density, poor flow property and sticking tendency to metal surfaces. Combination of such characteristics makes processing of tablets highly problematic, demanding the incorporation of suitable lubricants and glidants in the formulation. Added to these, the hydrolytic nature of fosinopril sodium further complicates the selection of other inert pharmaceutical excipients, particularly lubricants.

Conventional fosinopril sodium tablets were prepared using magnesium stearate as lubricant. However, these tablets were highly moisture sensitive and only marginally stable. Therefore, in order to achieve reasonable shelf lives, these required sophisticated protective packaging.

United States Patent Number 5,006,344 discloses that by eliminating magnesium stearate as the lubricant during the tabletting of fosinopril sodium and instead employing either sodium stearyl fumarate or hydrogenated vegetable oil tablets with improved stability were obtained.

In the present invention, we have discovered that use of a combination of talc and colloidal silicon dioxide during the tableting process as lubricant, surprisingly increase the stability of the tablet and provide reasonably long shelf lives.

Therefore, the present invention relates to a process for the preparation of a stable tablet comprising fosinopril sodium, optionally diuretic(s), and a combination of talc and colloidal silicon dioxide as lubricant. Conventionally colloidal silicon dioxide and talc are used as glidants but to our surprise the combination of two showed excellent lubricant properties. The tablets thus prepared by the process of the present invention had

improved shelf stability. Colloidal silicon dioxide or talc used individually in higher concentrations may also provide proper lubrication during processing of tablets and stability during storage. However, higher concentrations of lubricant would increase the tablet weight and may also exceed the permissible daily intake. Further, higher concentration of lubricant may also hamper the bioavailability of drug from the tablets. The combination of colloidal silicon dioxide and talc on the other hand has synergistic action and is therefore effective in reasonably low amounts. When used in combination the amount of talc may vary from about 0.25% to about 5% by weight, whereas that of colloidal silicon dioxide may vary from about 0.25% to about 10% by weight with respect to the total weight of tablet.

Present invention is further evident from the stability results generated at 40°C and 75% relative humidity over a time period of three months and at 60°C for one week (Table 1 & 2).

For the purpose of the present invention the tablets may contain fosinopril sodium alone or in combination with various diuretics. Suitable diuretics include chlorthalidone, thiazide diuretics, furosemide, triameterene, amiloride, spironolactone, and salts thereof. Thiazide diuretics may be selected from the group consisting of chlorothiazide, hydrochlorothiazide, flumethiazide, bendroflumethiazide and the like.

In addition to the actives (fosinopril sodium and optional diuretic), lubricants (talc and colloidal silicon dioxide), tablets prepared according to present invention may contain other pharmaceutically acceptable excipients such as diluents, disintegrants, binders, coloring agents and flavoring agents.

Diluents of the present invention may be selected from calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and mixtures thereof.

Binders of the present invention may be selected from methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl

cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, alginate and the like.

Disintegrant of the present invention may be selected from low substituted hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium A-type (Ac-di-sol), starch, crystalline cellulose, hydroxypropyl starch, partly pregelatinized starch and the like.

Coloring agents and flavoring agents may be selected from any FDA approved color and flavor which are compatible with all the other ingredients of the tablet.

The fosinopril sodium tablets of this invention can be prepared by conventional tablet making techniques such as wet granulation, dry granulation and direct compression.

For the wet granulation process, the fosinopril sodium alone or in combination with diuretics are blended with the diluent and disintegrant. This blend is then granulated with a solution of the binder in a solvent. The granules are then dried and sieved. The dried granules are mixed with talc and colloidal silicon dioxide and compressed into tablets.

In the direct compression process, the fosinopril sodium alone or in combination with diuretics is blended with the diluent, disintegrant and binder. The blend is then mixed with talc and colloidal silicon dioxide and compressed into tablets.

For dry granulation process, fosinopril sodium alone or in combination with diuretics is blended with diluent, binder and disintegant and compressed to form slugs. These slugs are milled to form granules. These granules are then mixed with talc and colloidal silicon dioxide and compressed into tablets.

The invention is further illustrated by the following examples but they should not be construed as limiting the scope of the invention anyway.

Example 1

Ingredients	mg/tab
Fosinopril Sodium	40.0
Anhydrous Lactose	90.0
Microcrystalline cellulose	40.0
Crospovidone	7.0
Povidone	10.0
Colloidal silicon dioxide	5.0
Talc	8.0
Isopropyl Alcohol	qs

Process:

1. Fosinopril sodium is blended with lactose, microcrystalline cellulose and a part of crospovidone.
2. The above blend is granulated with povidone solution in isopropyl alcohol.
3. The dried granules were dried and blended with crospovidone, talc and colloidal silicon dioxide and compressed into tablets.

Example 2

Ingredients	mg/tab
Fosinopril Sodium	20.0
Hydrochlorthiazide	12.5
Lactose Anhydrous	32.5
Microcrystalline cellulose	20.0
Crospovidone	3.5
Povidone	5.0
Colloidal silicon dioxide	2.5
Talc	4.0
Isopropyl Alcohol	qs

Process: Same as for Example-1

Example 3

Ingredients	mg/tab
Fosinopril Sodium	20.0
Hydrochlorthiazide	12.5
Lactose Anhydrous	97.5
Microcrystalline cellulose	40.0
Crospovidone	7.0
Povidone	10.0
Colloidal silicon dioxide	5.0
Talc	8.0
Isopropyl Alcohol	qs

Process: Same as for Example-1

Fosinopril tablets prepared as per Example-1 were tested for the initial amount of fosinopril sodium using HPLC. These samples were then kept at 40°C and 75% relative humidity for three months and at 60°C for one week. Amount of fosinopril at the end of first, second and third month was measured:

Table-1 Stability results generated at 40°C and 75% relative humidity over a time period of three months.

Tablets	Amount of Fosinopril sodium (mg)			
	Initial (mg)	After 1 month at 40°C and 75% relative humidity	After 2 month at 40°C and 75% relative humidity	After 3 month at 40°C and 75% relative humidity
Fosinopril tablets prepared as per the Example-1	40	39.69	39.98	39.23
" MONOPRIL" Commercially available fosinopril sodium tablets (strength- 40 mg) of BRISTOL MYERS SQUIBB	40.01	-	-	39.95

Table-2 Stability results generated at 60°C for one week

Tablets	Amount of Fosinopril sodium (mg)	
	Initial	After one week at 60^0 C
Fosinopril tablets prepared as per the Example-1	40.01	39.95
" MONOPRIL" Commercially available fosinopril sodium tablets (strength- 40 mg)of BRISTOL MYERS SQUIBB	40.01	39.79

WE CLAIM :

1. A process for the preparation of a stable tablet comprising fosinopril sodium, optionally diuretic(s), and a combination of talc and colloidal silicon dioxide as lubricant.

2. The process according to claim 1 wherein the diuretics may be selected from chlorthalidone, thiazide diuretics, furosemide, triameterene, amiloride, spironolactone, and salts thereof.

3. The process according to claim 2 wherein the thiazide diuretic are selected from the group consisting of chlorothiazide, hydrochlorothiazide, flumethiazide, bendroflumethiazide and the like.

4. The process according to claim 3 wherein the thiazide diuretic is hydrochlorothiazide.

5. The process according to claim 1 wherein talc is present in an amount of about 0.25% to about 5% by weight with respect to the total weight of tablet.

6. The process according to claim 1 wherein colloidal silicon dioxide is present in an amount of about 0.25% to about 10% by weight with respect to the total weight of tablet.

7. The process according to claim 1 wherein the tablet also comprises other pharmaceutically acceptable excipients.

8. The process according to claim 7 wherein the other pharmaceutically acceptable excipients are selected from the group consisting of diluent, disintegrant, binder, coloring and flavoring agent.

9. The process according to claim 8 wherein the diluent may be selected from group consisting of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and the like.

10. The process according to claim 9 wherein the diluent is lactose.

11. The process according to claim 8 wherein the binder may be selected from methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, alginate and the like.

12. The process according to claim 11 wherein the binder is povidone.

13. The process according to claim 8 wherein the disintegrant may be selected from low substituted hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium, starch, crystalline cellulose, hydroxypropyl starch, partly pregelatinized starch and the like.

14. The process according to claim 13 wherein the disintegrant is croscarmellose sodium.

15. The process according to claim 1 wherein the tablet is prepared by wet or dry granulation or direct compression.

16. The process according to claim 15 wherein the tablet is prepared by wet granulation.

17. The process according to claim 15 wherein the tablet is prepared by dry granulation.

18. The process according to claim 15 wherein the tablet is prepared by direct compression.

19. A process for the preparation of stable tablets of fosinopril sodium alone or with diuretic(s) comprising a combination of talc and colloidal silicon dioxide as lubricant, mixed with other pharmaceutically acceptable excipients substantially as described and illustrated by the examples herein.

Dated this 2ND day of AUGUST, 2002.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary